REMARKS

Claims 1-11 and 14-23 currently appear in this application. The Office Action of July 30, 2002, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Objections to Claims

Claim 14 is objected to as the subscripts in the primary oxidants are said to be unclear.

Accordingly, the present amendment submits claim 14 in a clear form.

Rejections under 35 U.S.C. 112

Claims 3, 13-17, 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. Claim 13 has been cancelled in favor of new claim 22, which claims a method for preparing a sol-gel porous material by chemically doping the material with stable

organic nitroxyl radicals. Claims 14-17 and 21 have now been amended to depend from claim 22.

With respect to the term "non-hydrolysable", original claim 7 of the PCT basic application read:

> The process according to any one of claims 1-5 wherein P is a non-hydrolysable substituent.

PCT claim 7 was inadvertently dropped in the amended set of PCT claims. For purposes of the present application, the terms "non-hydrolysable" and "non-polymerizable" are synonymous, in that polymerization occurs as a result of a hydrolysis reaction. Claim 1 has now been amended to recite that P is either a non-polymerizable group or a non-hydrolysable substituent.

Claim 23 deals with a process for using the catalyst of the present invention for the heterogeneous catalytic conversion of alcohols to oxidized derivatives thereof, particularly organic acids or aldehydes. This use is novel, and has now been made feasible according to the present invention by realization of a heterogeneous system (*i.e.*, biphasic, consisting of a solid catalyst (sol-gel on macroporous support) and liquid, the alcohol solution) with entrapped catalytic radicals, *i.e.*, stable, non-leachable, repeatably used catalysts. Support for claim 23 can be found in the language of

claims 1 and 13 (now cancelled) and examples 5, 6, and 7. Claims 14-17 and 21 have now been made to depend from claim 23.

Art Rejections

Claims 1-2, 4-11, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avnir in combination with Matsui et al. Avnir et al. are said to disclose doped sol-gel glasses. The Examiner concedes that Avnir et al. do not specifically disclose the use of a nitroxyl-containing or nitroxyl precursor containing dopant as part of the process. Matsui et al. disclose the use of TEMPOL, a potential nitroxyl precursor radical containing doping agent used as a probe to measure organic molecular trapping of organic molecules in the preparation and testing of doped sol-gel glasses. Matsui et al. are said to provide sufficient evidence that it is known in the art of doped sol-gel preparations to use nitroxide or nitroxyl precursors.

This rejection is respectfully traversed. Avnir et al. merely state that any organic molecule can be used to dope inorganic glasses. However, the only catalysts to be trapped within the glasses are enzymes (column 3, lines 61-68). Matsui et al. dissolve TEMPOL in a tetraethyl silicate sol-gel reaction system to dope the glass system. However, on page 274, right column,

Matsui et al. note that the TEMPOL possibly decomposed, resulting in weaker signal intensity. However, in the specification of the present application, Example 5 notes that the catalyst can be used, washed with cold water, and then used again, inferring that the nitroxyl radicals are stable within the glass.

Avnir et al. do not even suggest the use of materials other than enzymes for use as catalysts entrapped within sol-gel glasses. Matsui et al. note that the TEMPOL may have decomposed. Even though the Examiner alleges that the general reaction is old, there is no motivation for one skilled in the art to dope a sol-gel with stable organic nitroxyl radicals. One reading Matsui et al., noticing that the catalyst may have decomposed, certainly would not be motivated to use TEMPOL in a sol-gel as a catalyst, as there would be no way of knowing when the TEMPOL would decompose. Matsui et al. teach **away** from the present invention, and one skilled in the art, reading Matsui et al., would be motivated NOT to use TEMPOL in a sol-gel glass.

The present inventors have discovered that when the TEMPO nitroxyl radical moieties is entrapped in sol-gel glassy matrices, the resulting materials exhibit relevant catalytic oxidation properties, *i.e.*, they exhibit **high selective activity** in mediating oxidation of

alcohols **in different reaction media while being highly stable**, *i.e.*, reusable in several consecutive reaction runs with no leaching of the encapsulated materials into the liquid phase.

In short, **sol-gel materials doped with TEMPO are *new, high-performance selective oxidation catalysts* for the conversion of alcohols to valuable carbonyl and carboxyl compounds in the liquid phase.**

The following publications from peer-reviewed chemistry journals, copies of which are submitted herewith, describe the first applications *ever* reported of sol-gels doped with TEMPO for the catalytic oxidation of alcohols to form valuable carbonyls and carboxyl compounds.

Brunel et al., *Appiled Catalyst A: General* **213** (2001) 73-82

Ciriminna et al., *Advanced Synthesis & Catalysis* **334** (2002) 159-163

Ciriminna et al., *Chemical Communications* (2000) 1441-1442

Dijksman et al., *Chemical Communications* (2000) 271-272

Fey et al., *Journal of Organic Chemistry* **66:** 8154-8159 (2001)

Heeres et al., *Carbohydrate Research* **299** (1997) 221-227 (cited in Office Action)

Nooy et al., *Synthesis* (1996) 1153-1176

Sheldon et al., *Accounts of Chemical Research* **31** (1998) 485-493

The chemical properties of the catalysts of the present invention are new, unexpected, and highly valuable in terms of potential commercial applications of this discover. In fact, solid oxidation catalyst which are selective, stable, and versatile, and being actively researched worldwide because of their relevant commercial potential which is in direct contrast with the poor performance of most known inorganic and organic supports doped with active species used as oxidation catalysts [which are largely unstable in an oxidative environment, as shown by R. A. Sheldon et al, *Accounts of Chemical Research* **31** (1998) 485-493].

Specifically, most traditional heterogenization methods using TEMPO nitroxyl radicals on either organic or inorganic supports have been limited in scope when the resulting catalytic materials were used in real oxidation processes, such as the NaOCl oxidation of organic alcohols to carbonyls in biphasic systems (water/dichloromethane) or to the production of carboxylic acids in water.

For instance, TEMPO was recently *anchored* to the mesoporous channels of silica MCM-41 by Brunel et al., *Applied Catalysis A; General* **213** (2001) 73-82, and immobilized at the **surface** of the oligomeric triazine

Chimassorb 944 by oxidation of its amine moieties by Dijksman et al., *Chemical Communications* (2000) 271-272.

Oligoamine-supported TEMPO, as described above, could neither be employed in the presence of chlorinated solvents, where it readily dissolves, nor in the presence of metals such as Ru that readily coordinate to the amine moieties of the polymer. On the other hand, MCM-41-anchored TEMPO used in the NaOCl/NaBr oxidation of carbohydrates to carboxylates in water cannot be used in solutions above pH 8 to prevent dissolution of the delicate mesoporous MCM-41 a silica network in the liquid phase, with consequent leaching of the entrapped radicals in solution, as reported by Brunel et al., *supra*.

Adding to the general evidence of scope limitations of surface derivatization methods, the TEMPO moiety was also anchored on commercial aminopropyl-silica using 4-oxo-TEMPO and the catalyst formed was used in the NaOCl/NaBr oxidation of various alcohols in H_2O/CH_2Cl_2. However, as reported by Fey, Bolm et al., *Journal of Organic Chemistry* **68** (2001) 8154-8159, the catalyst was found to *progressively* lose its activity upon each oxidation run.

As reported by A. Heeres et al. in *Carbohydrates Research* **299** (1997) 221-227, an analogously anchored TEMPO silica catalyst applied to the

hypochlorite oxidation of the simple sugar glucose-1-phosphate in water lost 60% of its activity after a single oxidation run, and became *entirely inactive* after only two more runs, demonstrating the pronounced *instability* of such anchored catalyst in an aqueous alkaline oxidative environment.

These results demonstrate that, in contrast to homogeneous TEMPO, which is equally applicable to the rapid, high-yield conversion of a variety of alcohols in different reaction media as shown by deNooy et al., *Synthesis* 1996, 1153, heterogeneous TEMPO often *fails* to show analogous versatile activity, which, along with catalytic stability, are precise requirements of the fine chemicals industry.

After the priority application for the present application was filed in 1998, the present inventors have shown that by exploiting the versatility of the sol-gel process, *highly efficient* oxidation catalysts can be synthesized which are suitable for converting a vast class of organic alcohols in different reaction media, and which are *largely superior* to silica-supported TEMPO.

Thus, in collaboration with Bolm and Fey, the present inventors recently demonstrated in Ciriminna et al., *Advanced Synthesis and Catalysis* **344** (2002) 159-163, that sol-gel organically modified silica gels dopes with

TEMPO are *highly* stale and selective catalysts of the hypochlorite oxidation of alcohols to carbonyls, showing a *remarkable* stability in their selective activity, namely, a surprising "positive feedback" effect of their use, which is *unique* in this class of hybrid materials.

The present inventors had previously demonstrated that microporous sol-gel glasses doped with TEMPO according to the newly developed encapsulation process were *remarkably stable* and selective also in water when used in the NaOCl/NaBr conversion of D-methylglucose to the corresponding uronate, as reported by Ciniminna et al. in *Chemical Communications* (2000) 1441-1442.

It should be emphasized that it is the chemical *nature* of sol-gel glasses coupled with the mild character of common TEMPO-mediated oxidations, which are generally conducted at 0-4°C in the liquid phase with a multiplicity of suitable primary oxidants that ensures the remarkably stable activity and selectivity found using sol-gel glasses doped with TEMPO as oxidation mediators.

The sol-gel caging associated with the gelation process, in particular, chemically and physically *protects* the radicals within the cages, rather than leaving them unprotected at the surface of the material

as is the case with materials whose surface has been derivatized with an active chemical species. Moreover, the resulting doped glass as a whole acts as a *chemical sponge*, adsorbing and concentrating the reactants at the *surface of the cages*. It is precisely this unique feature of sol-gel materials that ensures the high stability of sol-gel encapsulated TEMPO.

Fey et al. have clearly demonstrated in *Journal of Organic Chemistry* 2001, **66**, 8154-8159, that the *progressive decrease* in the reactivity of silica-supported TEMPO is due to *intermolecular* quenching of the TEMPO radical moieties attached in proximity at the material surface, a phenomenon which is *intrinsically prevented* in the sol-gels of the present invention because of the sol-gel caging, as demonstrated by the present inventors in collaboration with Fey in the above-cited *Advanced Synthesis and Catalysis* article.

The importance of these findings may not be underestimated, considering, for instance, that despite said continuous decrease in the reactivity, silica gels functionalized with TEMPO with a process similar to that described by Fey et al in *Journal of Organic Chemistry* **66** (2001) 8154-8159, are currently being commercialized for the hypochlorite oxidation of alcohols in biphasic systems as described above by the chemical manufacturer

Sigma-Aldrich, *Chem-Files, Functionalized Silica Gels*, Aldrich (2002), **vol. 2, no. 6**, p. 15- product number 57,634-4. This is evidence of the commercial importance of even solid selective oxidation catalysts which have non-optimal performance in terms of life cycle and activity.

The present application is concerned with preparation and use of sol-gel glasses doped with the TEMPO radical moiety as high-performance oxidation catalysts. These catalysts are prepared by a process that uses 4-oxo-TEMPO as a suitable precursor in the presence of the species 2-aminopropyl-trimethyloxysilane and one or more silicon alkoxides as material precursors. This is neither disclosed nor suggested in Matsui et al., nor had it been reported previous to the filing of the instant application. Avnir et al. merely disclose preparing sol-gel materials doped with any tope of organic molecules, including enzymes. However, the simple encapsulation of an organic species within a sol-gel glass does not ensure that the resulting doped class will function as an effective chemical mediator.

Matsui et al. merely describe physico-chemical studies of the sol-gel process by ESR spectroscopy, in which the physical encapsulation of the 4-oxo-TEMPO in a sol-gel silica glass obtained by polycondensation of

tetraethoxysilane (TEOS) is followed in order to obtain information on the process itself, and on the nature of the microenvironment of the sol-gel silica cages. Organic nitroxyl radicals were used solely for the purpose of exploiting the paramagnetic "marking" properties of these radicals, and for their notable stability. There is nothing in Matsui et al. that even suggests that these sol-gel glasses can be used for chemical applications.

As the Federal Circuit stated in *In re Lee*, 61 USPQ2d 1430 (January 18, 2002, Fed. Cir.), "As applied to the determination of patentability *vel non*, when the issue is obviousness, 'it is fundamental that rejections under 35 U.S.C. 103 must be based on evidence comprehended by the language of that section.' *In re Grasselli*, 53 USPQ2d 1769, 1774 (Fed. Cir. 2000)… When patentability turns on the question of obviousness, the search for an analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness *See, e.g., McGinley v. Franklin Sports, Inc*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ('the central question is whether there is a reason to combine [the] references,' a question of fact drawing on the *Graham* factors."

'The factual inquiry whether to combine references must be thorough and searching.' *Id.* This precedent has been reinforced in myriad decisions, and cannot be dispensed with, *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.,* 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). ('a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential component of an obviousness holding"') (quoting *C. R. Bard, Inc. v. M3 Systems, Inc.* 48 USPQ2d (Fed. Cir. 1998)) The Court went on to quote *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."

There is a requirement for specificity in combining references, *See, In re Kotzab*, 55 USPQ2d 13134, 1317 (Fed. Cir. 2002)("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."). Since Ogawa et al. teach **away** from incorporating nitroxyl radicals in a sol-gel, it is respectfully submitted that the claims at bar are patentable.

In conclusion, the present inventors have discovered and developed a vast class of effective solid oxidation catalyst suitable for converting a large class of alcohols into valuable carbonyls and carboxylic acids. These catalysts contain the TEMPO radically moiety chemically or physically linked to the cages of highly porous inorganic or hybrid organic-inorganic oxides whose chemical and physical properties can be tailored to meet the requirements of one or more chemical conversion processes.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable consideration is earnestly solicited.

Respectfully submitted,

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IN THE SPECIFICATION

Page 14, please amend the fourth paragraph beginning on line 21 as follows:

The chemical entrapment of the nitroxyl radicals was carried out in 2 steps. The catalyst is prepared by anchoring the nitroxyl radical through the oxo group of 4-oxo-TEMPO to the amino group of aminopropyltrimethoxysilane and further polymerizing the resulting monomer with an acidic sol of ~~tetramethoxyortosilicate~~tetramethoxyorthosilicate (TMOS,$Si(OCH_3)_4$). After 24h stirring a solution of 4-oxo-TEMPO (424 mg) in methanol (3 mL) with aminopropyltrimethoxysilane ($H_2N-(CH_2)_3-Si(OCH_3)_3$, 480 mL, 10% molar excess) the resulting alcoholic immine is mixed with a portion of acidic sol stock TMOS solution previously prepared by mixing TMOS (29,5 mL), H_2O (3.6 mL), MeOH (32,40 mL) and HCl IN (140 µl). Thus, a portion of the sol stock mixture (3.28 mL) was partially neutralized with NH_4OH 0.1 M (69.8 µL) and mixed together with 1.14 mL of the immine precursor solution. Methanol (7.41 mL) was subsequently added under stirring followed by H_2O (3.88 mL) to promote hydrolysis and condensation. As a formal acidity measure, pH (6.0) refers to the concentration of hydrogen ions in the total volume. The

resulting mixture (Si:H_2O:MeOH=1:5.5:6) gelled rapidly (10 min) in a transparent, elastic alcogel coloured in orange which was left at ambient temperature for 3 days and subsequently dried at 50°C resulting in a monolithic doped xerogel of 0.93 g. The sol described above was dried by removing the solvent under reduced pressure (15mm Hg) affording an orange areogel powder.

Page 17, please amend the first paragraph beginning on line 2 as follows:

The catalytic activity of the sol-gel materials doped with nitroxyl radical thus far described was tested in different oxidative runs using α-D-methylglucopyranoside and trans-cinnamyl alcohol as substrates along with aqueous hypobromite and CuCl/air as primary oxidants, respectively. In a typical sugar oxidation they catalytic oxidation reaction was carried out by adding granules of the doped materials (e.g. 0.247 g of a catalyst 3.70% (w/w) in TEMPO, or 0.352 g of a catalyst 3.24% (w/w) in 4-oxo-TEMPO) to an aqueous, solution of methyl-α-D-glucopyranoside (MGP, 1.0 g) and sodium bromide (0.10 g) in 200 mL H_2O at 4°C. A cold hypochlorite solution (10 mL, 10% w/w) previously brought to pH 10 by adding 4M HCl, was then added at once. The pH was kept constant at 10 by adding 0.5M NaoH in order

to neutralize the acid released during the reaction. When the oxidation was completed (no more acid formation, typically 40 min), the reaction mixture was quenched by adding 96% ethanol (4 mL) and by changing the pH to 6 by addition of 4M HCl. The catalyst was filtered, and the product (sodium ~~methyl-α-D-glucopyranosiduronate~~methyl-α-D-glucopyranosideuronate) was obtained from the filtrate by freeze-drying in a lyophylizer. The yield of the reaction was practically quantitative. For the next reaction cycle, the catalyst was washed with cold water and reused as such under the same conditions described above. The catalyst was reused in 3 subsequent similar oxidation runs of the same substrate MGP with minor decrease in activity. The elemental analysis after oxidative runs did not detect any nitrogen, thus establishing the lack of leaching of the entrapped nitroxyl radicals in the reaction solution.

IN THE CLAIMS

Please amend claim 1 as follows:

1. (Twice Amended) A process for the preparation of reactive sol-gel catalytic porous materials either chemically or physically doped with stable organic nitroxyl radicals, comprising the steps of:

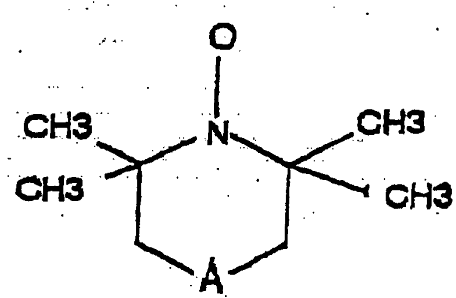
a) copolymerizing a solution including:

at least one monomer precursor selected from the group consisting of metal and semi-metal alkoxides, metal esters and semi-metal esters, of the general formula

$$M(R)_n(P)_m$$

wherein M is a metal or a semimetal, R is an hydrolysable substituent, P is a non-polymerizable group **or a non-hydrolyzable substituent**, n is an integer of 1 to 6, and m is an integer of 0 to 6,

a dopant consisting of a stable di-tertiary-alkyl nitroxyl radical or a precursor thereof of formula



wherein A represents a chain of two or three carbon atoms, one or two of said carbon atoms being eventually substituted by one oxygen or nitrogen atom,

a solvent including H_2O and a co-solvent selected from the aliphatic alcohols;

an acid or base to catalyse the processes of sol-gel hydrolysis and copolymerization; and

one or more additives selected from those known to be useful in the preparation of porous materials

to form a gel containing said dopant trapped therein;

b) evaporating said solvent;

c) drying said gel;

d) coating said gel on a mesoporous inorganic support; and

e) drying said mesoporous material coated with said sol-gel.

3. (Third Amendment) The process according to claim ~~19~~22, wherein said non-hydrolyzable substituent is H, an alkyl, aryl or fluoroalkyl group or an aminoalkyl group.

4. (Third Amendment) The process according to claim ~~1~~22, wherein said step c) of drying the gel is a liophilisation carried out at a pressure lower than 70 mm Hg, to obtain a mesoporous aerogel powder.

5. (Third Amendment) The process according to claim ~~1~~22, wherein said step c) of drying the gel is a mild heat treatment carried out at an atmospheric pressure and a temperature no greater than 100°C.

6. (Amended) The process according to claim ~~1~~22, wherein said nitroxyl radical is added to said solution along with said monomer precursor in a one-step procedure.

7. (Amended) The process according to claim ~~1~~22, wherein in a two-step procedure, first said monomer precursor is hydrolyzed in part with water in the presence of an acid and then said nitroxyl radical is added to this solution, to obtain a porous sol-gel polymeric oxide with a fractal macromolecular structure.

9. (Amended) The process according to claim ~~8~~22, wherein said ~~radical is tethered to said monomer precursor through~~ reductive amination **is carried out** by stirring ~~for three hours~~ a solution of **said** 4-oxo-TEMPO in methanol with ~~a slight excess of~~**said** 3-aminopropyl-trimethoxysilane, and reducing the thus formed imine with $NaBH_3CN$.

11. (Twice Amended) The process according to claim ~~1~~22, wherein said catalytic porous materials are in the shape of powders, films, monoliths, or fibers.

14. (Amended) A process according to claim ~~13~~23, wherein said liquid phase is an organic solvent, a biphasic organic solvent-water system, or water and said primary oxidant is NaOCl, NaOBr, ~~HNO_3~~HNO_3, ~~$CuCl/O_2$~~$CuCl/O_2$, ~~$K_3Fe(CN)_6$~~$K_3Fe(CN)_6$, or ~~NO_2~~NO_2.

15. (Third Amendment) A process according to claim ~~13~~23, wherein said alcohol substrate is an alkyl alcohol, an aryl alcohol, a steroid alcohol, an allylic alcohol, a terpenoid alcohol or retinol and it is ~~oxidated~~ oxidized in a bi-phasic reaction system CH_2Cl_2-H_2O, said primary oxidant is aqueous alkaline NaOCl and wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-aminopropyl-trimethoxysilane to obtain a catalytic material containing chemically linked radicals.

16. (Twice Amended) A process according to claim ~~13~~23, wherein said alcohol substrate is a monomer or an oligomeric carbohydrate protected at the anomeric center, said solvent is water, said oxidant is alkaline NaOCl or NaOCl in the presence of a catalytic amount of NaBr, and wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-amino-propyl-

trimethoxysilane to obtain a catalytic material containing chemically linked radicals.

18. (Twice Amended) The catalytic material doped with a chemically linked nitroxyl radical obtained with a process as claimed in claim ~~8~~22.

21. (Amended) A process according to claim ~~13~~23, wherein said alcohol substrate is an alkyl alcohol, an aryl alcohol, a steroid alcohol, an allylic alcohol, a terpenoid alcohol or retinol and it is oxidated in a bi-phasic reaction system CH_2Cl_2-H_2O, wherein said primary oxidant is aqueous alkaline NaOCl, and wherein said nitroxyl radical is 4-oxy-TEMPO and said monomer precursor is 3-aminopropyl-trimethoxysilane to obtain a catalytic material containing chemically linked radicals, wherein said radical is tethered to said monomer precursor through reductive amination by stirring for three hours a solution of 4-oxo-TEMPO in methanol with a slight excess of 3-aminopropyl-trimethoxysilane, and reducing the thus formed imine with $NaBH_3CN$.